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ORIGINAL SUBMISSION

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GRN 000066

JHB Inc.
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This notification is offered to show exemption from the premarket approval requirements of the Federal Food and Drug Administration for the use of 2.5ml of the botanical extract Milk Thistle (Silybum marianum, 2.5ml extract = 50 mg silymarin) as an ingredient per 355ml serving of a malt based beverage (beer), and prove its status as "Generally Regarded As Safe" based on scientific procedures as determined by JHB Inc.

Milk Thistle Extract Preparation

Brucia Plant Extracts, Inc., a leader in quality botanical preparations since 1975, produce the Milk Thistle extract.

Personnel

1. All individuals engaged in quality control are conversant with herbal terminology and have expertise in:
   1.1 the identification of Milk Thistle
   1.2 the recognition of possible adulterants, terrestrial contaminants, fungal and insect infestations
   1.3 the determination of non-uniformity within the differences in quality between consignments of plant materials.
2. Personnel working in storage areas are apprised of, and provided appropriate training in the handling of raw materials

Raw Material Testing

1. Specifications for medicinal plant materials include the following:
   1.1 botanical identity, including genus, species and authority(e.g., Silybum marianum);
   1.2 detailed information on
      1.2.1 geographical source;
      1.2.2 cultivation and collection techniques;
      1.2.3 time of harvest;
      1.2.4 biological age
      1.2.5. nature and extent of artificial fertilizers, pesticides, herbicides, insecticides and fumigants, etc., if used;
      1.2.6 nature and extent of radioactive residues, if applicable

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1.2.7 where processing cannot be initiated prior to 8 hours after harvesting, Milk Thistle seeds are stored under conditions that are appropriate for conservation

Chemistry and Pharmacology

Milk Thistle seeds contain 1.5-3% flavoneligands, collectively referred to as silymarin (Bruneton, 1995; Wichtl and Bisset, 1994); 20-30% fixed oil, of which approximately 60% is lenoleic acid, approximately 30% is oleic acid, and approximately 9% is palmitic acid; 25-30% protein; 0.038% tocopherol; 0.63% sterols. Including cholesterol, campesterol, stigmasterol, and sitosterol; and some mucilage (Meyer-Buchtela, 1999; Wichtl and Bisset, 1994). The three principle components of silymarin are the flavanoligans silybin, silychristin, and silidianin (Bruneton, 1995; Leung and Foster, 1996; Wichtl and Bisset, 1994).

Liquid Extract

The Milk Thistle extract is produced using a Maceration/Percolation process with certified organic isolated crushed Milk Thistle seed husks (seed freed from pappus), pure grain alcohol, and purified water in accordance with the Good Manufacturing Practices of Herbal medicinal products. The finished liquid Milk Thistle extract consists of approximately 100 mg silymarin (as determined by USP spectrophotometric assay method) per 5ml of 66% pure grain alcohol.

The liquid extract is stored in sterilized glass containers, in a cool, dark environment appropriate for conservation.

Use of Liquid Milk Thistle Extract

The finished Milk Thistle extract is used as an ingredient in a traditional style malt based beverage (2 row malt, nugget hops, munich malt, carmel malt 6-90). The Milk Thistle extract is mixed with the brewed beverage in a finishing tank directly prior to bottling. Each 355ml glass bottle serving will contain approximately 2.5 ml of Milk Thistle extract (50 mg silymarin). The Milk Thistle Extract is used as a flavor enhancer, particularly as a bittering agent.

Overview

The milk thistle of commerce is a standardized preparation extracted from the fruits (seeds) of Silybum marianum (L.) Gaertn., Asteraceae (syn. Carduus marianus L.), a plant native to the Mediterranean. The leaves have been used since Greco-Roman times as an herbal remedy for a variety of ailments, particularly liver problems. Eclectic physicians in the United States in the latter nineteenth and early twentieth centuries

acknowledged the clinical benefits of preparations from the milk thistle seeds (technically the fruits) for "Congestion of the liver, spleen, and kidneys ..." (Felter and Lloyd, 1983). It is widely used in German phytotherapy for "chronic hepatitis of all types," and especially for fatty liver (cirrhosis) associated with alcoholics (Weiss, 1988).

Milk thistle is an example of a preparation that is required to be in the standardized, concentrated form in order to fully convey the desired, in this case, hepatoprotectant, effects. Milk thistle preparations are usually standardized to a concentration of 70 to 80% of three flavonolignans (silibinin, silychristin, and silydianin), collectively known as silymarin. According to research conducted by the original manufacturer and primary researcher of milk thistle extract, Madaus AG of Cologne, Germany, this level of concentration of silymarin is required to survive degradation by gastric fluids and in order to enter into the bloodstream via the intestinal wall. Silymarin is poorly absorbed (20–50%) from the gastrointestinal tract; thus, the concentrated extract is recommended (Foster and Tyler, 1999; Robbers and Tyler, 1999).

The original product in Germany contains 70 mg silymarin. The Commission E approved uses and the subsequent use of milk thistle standardized extracts in the United States are based on a significant amount of chemical, pharmacological, and clinical research. There have been an estimated 120 clinical studies carried out on the proprietary milk thistle preparation from Madaus, known in Germany as Legalon®. A comprehensive and detailed review of the pharmacokinetics and clinical pharmacology of Legalon® has been published in English by the manufacturer (Anon., 1989).

Clinical studies suggest or confirm the efficacy of milk thistle extract for various hepatic disorders, including hepatitis A, alcoholic cirrhosis, and exposure to hazardous chemicals. Another relatively esoteric use is as a preventive and/or antidote to poisoning by the deathcap mushroom, Amanita phalloides. A preparation of the silibinin fraction is available in Germany as an intravenous (i.v.) drip for such acute cases.

A primary use for silymarin is in the treatment of liver damage due to ingestion of alcohol. An early double-blind study examined 66 patients, most with alcohol-induced toxic liver disease (Fintelmann and Albert, 1980). The 31 patients who received 420 mg/day of Legalon® showed a significant influence on serum levels of glutamic-oxalacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), and Gamma-GT over those 35 patients receiving placebo, with levels returning to normal more quickly in the treated group than placebo. Another double-blind study with 36 patients suffering from alcohol-induced liver disease found that pathological liver parameters (GOT, GPT, Gamma-GT, and bilirubin) were significantly reduced in the patients receiving

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silymarin (Legalon®) after six months of treatment compared to the placebo group (Feher et al., 1990). In another study, a randomized, controlled trial was performed to determine the effect of silymarin in the treatment of patients with alcohol- and non-alcohol-induced cirrhosis (Ferenci et al., 1989). Of the 170 patients, 87 received 420 mg of silymarin daily, compared with 83 placebo patients. The mean observation period was 41 months, with 10 dropouts in the placebo group and 14 in the treatment group. The four-year survival rate was 58+/-9% in the silymarin-treated patients, and 39+/-9% in the placebo group (p=0.036). No adverse side effects of drug treatment were observed.

In another double-blind, controlled study, the effects of silymarin on chemical, functional, and morphological alterations of the liver were examined (Salmi and Sarna, 1982). The 106 patients with liver disease in the study were selected on the basis of elevated serum transaminase levels. A total of 97 patients completed the four-week trial (47 treated and 50 placebo). A dose of 420 mg a day of silymarin produced a statistically significant greater decrease of GPT and GOT liver enzymes in the treated group than in the control. Serum total and bilirubin decreased more in the treated than in the control group, but the differences were not statistically significant.

Some forms of hepatitis have responded to silymarin treatment. A study reported on 67 subjects treated as outpatients for toxic metabolic liver damage, chronic hepatitis, and bile duct inflammation (Poser, 1971). After three months of treatment (525 mg/day of silymarin), chronic hepatitis was found to be significantly improved bioptically. Conditions associated with bile duct inflammation also responded particularly well. Another double-blind study looked at the effect of silymarin in the treatment of acute viral hepatitis (Magliulo et al., 1978). A daily dose of 420 mg therapeutically influenced the increased serum levels of bilirubin, GOT, and GPT characteristically associated with acute viral hepatitis. After five days of treatment, the laboratory parameters regressed more in the treated group than for the placebo group. After three weeks, more patients in the treated group had attained normal values than in the placebo group. A statistical analysis showed a difference between GOT and bilirubin values in the silymarin and placebo groups, with a regression of GPT values in favor of silymarin. A recent case report of chronic infection by hepatitis B virus and hepatitis C virus demonstrated potential efficacy of treatment with milk thistle (10 g ground-up seeds in oatmeal with standardized (70%) milk thistle extract capsules three times daily) in combination with another herb known for its hepatoprotectant activity, Phyllanthus amarus (200 mg, three times daily) (McPartland, 1996). In a review of important European clinical studies ranging from 1971 to 1988 (including those summarized above), the authors found the data suggests the effectiveness of silymarin not only in toxic and metabolic liver damage, but also in acute and chronic hepatitis (Hikino and Kiso, 1988). Silymarin's ability to stabilize the cell membrane and

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stimulate protein synthesis, while accelerating the process of regeneration in damaged liver tissue, was found to be important in its therapeutic efficacy.

The hepatoprotectant effect of milk thistle fractions (silymarin) is documented in other studies: these compounds can produce both a protective and curative effect on liver damage resulting from the highly toxic compounds phalloidin and alpha-amanitin (from the deathcap mushroom, A. phalloides). A multicenter trial conducted from 1979 to 1982 involved 220 cases of Amanita poisoning treated in German, Swiss, and Austrian hospitals (Hruby, 1984). Silibinin (administered i.v.) in supportive treatment was used. The mortality rate was 12.8%, compared to a mortality rate of 22.4% in a study where only 16 of the 205 patients were treated with 20 to 50 mg/kg/day of silibinin (Floersheim et al., 1982). Hruby concluded that the use of silibinin in addition to current methods of treating Amanita poisoning could lower mortality rates below any previously achieved.

A literature review noted that Legalon® is the best-documented agent for the treatment of toxic liver impairment (Morazzani and Bombardelli, 1995). These authors also reviewed studies which suggest future use in dermatological and cosmetic products, based on a number of activities including promoting healing at wound sites, improved burn healing, and counteracting skin degeneration and aging via anti-inflammatory and free radical scavenging mechanisms. A more recent review concluded that despite some flaws in methodology of some of the clinical studies, Legalon® has not demonstrated adverse side effects and it "may be effective in improving the clinical courses of both acute and chronic viral, drug- and toxin-induced and alcoholic hepatitis" (Flora et al., 1998).

Because the well-documented antioxidant activity of silymarin has been shown to prevent lipoperoxidative hepatic damage by xenobiotic compounds (e.g., alcohol and certain pharmaceutical drugs), researchers attempted to determine whether milk thistle would be helpful for patients being administered psychotropic drugs. In a double blind, placebo-controlled study, the efficacy of silymarin was evaluated in-patients receiving psychotropic drugs as long-term therapy (Palasciano et al., 1994). Sixty women in the psychiatric ward of an Italian hospital were selected for the trial, all having been treated with either phenothiazines and/or butyrophenones for at least five years. They were randomly divided into four groups, with the silymarin patients receiving 800 mg a day for 90 days. Results showed that 800 mg/day of silymarin may be useful in the treatment of some instances of lipoperoxidative hepatic damage, such as the damage that may occur during long-term treatment with the psychotropic drugs.

The therapeutic activity of silymarin is based on two sites or mechanisms of action:

(a) It alters the structure of the outer cell membrane of the hepatocytes in such a way as to prevent penetration of the liver toxin into the interior of the cell. (b) It stimulates the action of nucleolar polymerase A, resulting in an increase in ribosomal protein synthesis, and thus stimulates the regenerative ability of the liver and the formation of new hepatocytes.

Milk thistle extract provides hepatocellular protection by stabilizing hepatic cell membranes (McPartland,1996). Other actions include interruption of enterohepatic recirculation of toxins, stimulation of protein synthesis and regeneration of damaged hepatocytes, as well as antioxidant activity (McPartland, 1996).

Recent research on silibinin and silichristin to promote faster regeneration of diseased liver tissue has focused on the ability of silibinin to stimulate the activity of the DNA-dependent RNA-polymerase I, causing an increase in rRNA synthesis and an accelerated formation of intact ribosomes. This results in a general increase in the rate of synthesis of all cellular proteins. In vivo and in vitro molecular modeling experiments indicate that silibinin may imitate a steroid hormone by binding specifically to polymerase I, thus stimulating enzyme activity (Sonnenbichler et al., 1998).

Contraindications

None known.

Side Effects

None known.

Formulations: A mild laxative effect has been observed in occasional instances.

Interactions with Other Drugs

None known.

Summary

Milk Thistle extract has become increasingly popular in the United States as a dietary supplement. Based on the existing and increasing number of clinical studies indicating its safety and suggesting efficacy, JHB Inc. recognizes 2.5 ml of Milk Thistle extract (50 mg silymarin) per serving as GRAS and complimentary when added to a malt based beverage. The data and information that are the basis for the GRAS determination are available for review and copying by the FDA or will be sent to the FDA upon request.

December 14, 2000

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Note

This material was adapted from The Complete German Commission E Monographs-Therapeutic Guide to Herbal Medicines and onhealth with webmd. M. Blumenthal, W.R. Busse, A. Goldberg, J. Gruenwald, T. Hall, C.W. Riggins, R.S.Rister (eds.) S. Klein and R.S. Rister (trans.). 1998. J. Hill 2000.

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